Metformin as an Adjuvant Treatment in Non-Diabetic Metastatic Breast Cancer

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Highlights

• Radiological response was significantly better in the metformin group than the control group (overall P = 0.002).
• Metformin did not significantly prolong OS (HR = 0.57, CI 0.24–1.3); however, OS was better in the metformin vs. control group (5.3 vs. 5.8 months).
• Metformin did not significantly prolong PFS (HR = 0.311, CI 0.063–1.5); however, OS was better in the metformin vs. control group (4.4 vs. 5.1 months).

Background: Mounting evidence suggests that metformin halts cancer spread and acts as an antimetastatic drug.

Patients and Methods: Fifty women diagnosed with stage IV breast cancer were allocated randomly into two groups. The control group received chemotherapy and the metformin group received metformin plus chemotherapy for 3 months. Main outcome included measuring changes in tumors using Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate disease progression before and after 3 months, whereas secondary outcomes included, overall survival (OS) and progression free survival (PFS).

Results: The control group had a significantly worse RECIST response rate than the metformin group. The metformin group had a slightly longer OS and higher PFS than the control group, but this difference was not statistically significant. Hazards of mortality and disease progression were reduced with metformin use.

Conclusion: Metformin use significantly improved the radiologic response rate in nondiabetic patients with metastatic breast cancer but did not significantly prolonged OS or PFS. Our results suggest that randomized clinical trials in patients with metastatic breast cancer are warranted.

Clinical Trial.gov ID: NCT04143282

Key words: Metformin, Stage IV breast cancer, Radiological Response

INTRODUCTION

Breast cancer is the most common cause of death in women with cancer. The 5-year relative survival rate for breast cancer is approximately 90% in women; highest and lowest rates of survival favored localized and metastatic breast cancer, respectively[1]. Metastatic breast cancer is an aggressive and complicated disease; approximately 6% of women who came in for the first consultation were diagnosed with metastatic breast cancer[2], with an 5-year overall survival (OS) of nearly 27%[3]. A crucial element in treatment failure in metastatic breast cancer includes non-responsiveness to chemotherapy, which is attributed to drug resistance[4]. Improving chemotherapy sensitivity through different mechanisms, which include but are not limited handling gene resistance[5], interruption of glucose supply[6], use of novel drug delivery system[7], and addition of an adjuvant medication to reduce resistance by blocking specific or multiple steps in cancer cell proliferation[8], is vital for survival. Metformin is one of the most commonly used antidiabetic agents due to its safety and cost effectiveness[9]. Preclinical studies focus on the ability of metformin to reduce cancer cell burden[10]. Use of novel drugs to stop disease progression and provide targeted therapy may be costly, with side effects that cannot be tolerated. A combination of therapy, sometimes needed in advanced disease, may provide more synergistic effect in certain cases. Metformin is known to inhibit cancer cell proliferation through different molecular mechanisms, including inhibition of the insulin signaling pathway (insulin/IGF-1)[11,12]. However, some cases develop resistance to chemotherapy by altering both mechanisms, namely AMPK and insulin/IGF-1 pathways[13], which are vital for altering chemotherapy resistance, for example, the activation of AMPK leads to cancer cell apoptosis through the activation of the tumor suppressor P53[14]. This gene regulates therapy-induced cellular senescence, thereby inhibiting cancer cell proliferation, leading to slowdown of protein synthesis[15,16]. The inactivation of the IGF-1 pathway results in a reduction of glucose absorption, which finally, promotes apoptosis[17]. Studies have shown promising evidence supporting the role of metformin as an adjuvant treatment in different cancer types[18-20]. This investigation is an interventional study to evaluate if metformin, as adjuvant therapy along with standard chemotherapy, improves survival in nondiabetic patients with stage IV breast cancer.

PATIENTS AND METHODS

This study is a randomized control clinical trial registered at clinicaltrials.gov (#NCT04143282). Ethics approval was obtained from

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the local ethics committee. Fifty-nine patients with radiologically and clinically confirmed stage IV breast cancer were enrolled in the trial, based on our inclusion and exclusion criteria (Figure 1). Patients signed a consent form before starting the trial according to the guidelines of the ethics committee. Inclusion criteria included nondiabetic patients who met the following criteria: 1) radiologically confirmed metastatic breast cancer (stage IV) and 2) age between 18–75 years. Exclusion criteria were as follows: 1) hypersensitivity to metformin, 2) patients diagnosed with diabetes before or after the trial, 3) any medical condition that increased lactic acidosis, and 4) patients with metastatic breast cancer who were on hormonal treatment.

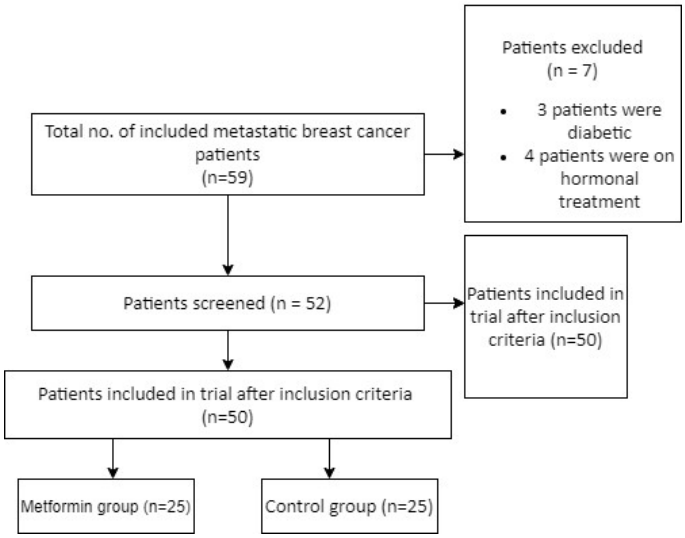

Figure 1: Flow chart of patient selection according to exclusion and inclusion criteria

Data, including clinical characteristics, such as age, weight, history of hormonal contraceptives, and body mass index (BMI), which is classified into two main categories at a cut off = 25 kg/m^2[21], were collected from the patient's files.

In addition, data on metastatic breast cancer diagnosis, including tumor site, tumor size, pathologic stage, estrogen/progesterone / human epidermal growth factor-2 receptor status (ER/PR/HER2), time from initial presentation to metastasis and disease, and menopause status, were collected. Radiologic response rates were evaluated before and after 3 months of standard chemotherapy in both control and metformin groups (standard chemotherapy plus metformin, 1 g twice daily)[22]. We used Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria to evaluate the response of tumor to treatment; in control and metformin groups, chemotherapy alone and chemotherapy plus metformin, respectively, were administered to patients with breast cancer and distant metastasis (Table 1)[23]. Moreover, OS and progression free survival (PFS) were calculated and defined as Food and Drug Administration (FDA) them at endpoints of clinical trials[24]. Chemotherapy included gemcitabine plus carboplatin[25]; anthracycline based chemotherapy regimens, mainly the FAC protocol (fluorouracil, doxorubicin, and cyclophosphamide, 21-d cycle)[26]or AC (doxorubicin and cyclophosphamide, 3-week cycle)[27]; vinorelbine (3-week cycle)[28]; capecitabine (3-week cycle)[29]; paclitaxel (3-week cycle)[30]; and taxanes-based regimens, including gemcitabine plus paclitaxel (3-week cycle)[31]. The most frequent side effects of chemotherapy, including febrile neutropenia, anemia, and gastrointestinal disorders, were scored using the Common Terminology Criteria for Adverse Events (CTCAE); moreover, metformin-related side effects were evaluated[32].

Table 1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[23]

Complete response (CP)	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
Partial response (PR)	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline
Progressive disease (PD)	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded OR The appearance of new lesions, including those detected by FDG-PET
Stable disease	Criteria not applied to PD or PR

FDG-PET: fludeoxyglucose positron emission tomography

STATISTICAL ANALYSIS

Data analysis was performed using SPSS v. 25 (Statistical Package for Social science). For descriptive statistics, mean and standard deviation (SD) were calculated, and for other variables they were presented as total number (No.) and percentage (%). The chi-square was used to test significant differences in categorical data, independent t-test to test differences for scale data, and paired t-test to follow up changes in scale variables. We used the Kaplan–Meier test to obtain median of survival and log-rank test to test differences in survival duration, and 95% confidence interval (CI) and hazard ratio (HR) were calculated for PFS. Results were significant when P-value ≤ 0.05.

RESULTS

We found no difference in clinical features and characteristics including age, weight, and contraception history, between the two groups (Table 2).

Table 2: Baseline patient characteristics of control and metformin groups

Characteristics	Control Group	Metformin Group
Age (Mean±SD)	49.2 ± 11.7	48.8 ± 9.4
Weight (Mean±SD)	71.7 ± 14.3	71.4 ± 14.1
History of hormonal contraception, *N* (%) No	9(36)	8(32)
History of hormonal contraception, *N* (%) yes	16(64)	17(68)
Pre-menopausal *N* (%)	12(48)	10(40)
Post-menopausal *N* (%)	13(52)	15(60)
BMI <25 kg/m2	10(40)	11(44)
BMI>25 kg/m2	15(60)	14(56)

In addition, no differences regarding disease characteristics, pathological grades, metastatic sites, number of metastatic sites, and time from 1ry disease till metastasis were observed. However, in pathological grades, both groups were likely to be grade II (92% and 96% in control and metformin groups, respectively). Both groups exhibited multiple metastatic sites (44% for both groups) rather than bone or visceral metastasis alone. The number of metastatic sites was mostly two (48% vs. 56% in control and metformin groups, respectively). However, most patients were HER2 negative (72%) in both groups and likely to be ER/PR positive (80% in both groups) (Table 3).

Table 3: Baseline disease characteristics of control and metformin groups

Disease	Control Group *N* = 25(%)	Metformin Group *N* = 25(%)
Pathological grades		
II	23(92)	24(96)
III	1(4)	1(4)
IV	1(4)	0(0)
Metastasis site		
Bone	7(28)	6(24)
Visceral	7(28)	8(32)
Multiple	11(44)	11(44)
No of metastasis sites		
1	12(48)	14(56)
2	9(36)	8(32)
More than two	4(16)	3(12)
Time from 1ry disease till metastasis		
Initially metastatic	9(36)	10(40)
1 month to 5 years	12(48)	13(52)
5 years to 10 years	4(16)	2(8)
HER2 Negative	18(72)	18(72)
HER2 Positive	7(28)	7(28)
ER/PR Negative	5(20)	5(20)
ER/PR Positive	20(80)	20(80)

Regarding recorded adverse events, no difference, except for diarrhea grade 1 (8% vs. 36%), was observed between control and metformin groups, respectively (Table 4).

Table 4: The reported toxicity and adverse events in each group

Type of adverse event	Control Group *N*=25(%)	Metformin Group *N*=25(%)
Nausea and vomiting		
Grade 1	10(40)	15(60)
Diarrhea		
Grade 1	2(8)	9(36) *
Neutropenia		
Grade 3	10(40)	7(28)
Grade 4	5(20)	3(12)
Anemia		
Grade 3	10(40)	7(28)
Grade 4	4(16)	3(12)

Our findings revealed that women with stage IV breast cancer, treated with metformin plus chemotherapy (metformin group) had significantly better radiologic (RECIST) response rate than women in the control group who received chemotherapy only (overall *P*-value = 0.002) (Figure 2).

The mean of follow up duration was 6 months, death was confirmed in 8 out of 50 patients (24% vs. 8%) in control and metformin groups, respectively, mean OS values were 5.3 vs. 5.8 months for control and metformin groups, respectively (Figure 3).

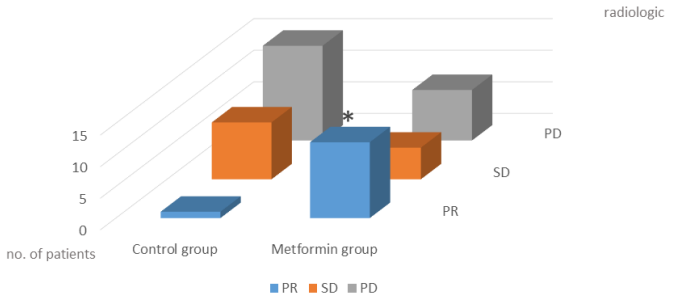

Figure 2: The Association between metformin use and radiological response to standard chemotherapy in non-diabetic women with metastatic breast cancer
*Significantly different from control group at $p < 0.05$
PR=partial response, SD=stable disease, PD=progressive disease

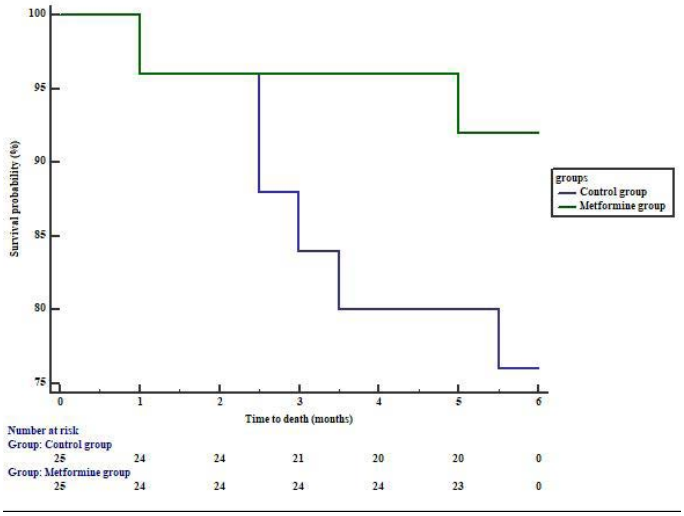

Figure 3: Kaplan-Meier curve of overall survival

We noticed progression of disease in 23 out of 50 patients (60% vs. 32%) for control and metformin groups, respectively; mean PFS was 4.4 vs. 5.1 months for control and metformin groups, respectively (Figure 4).

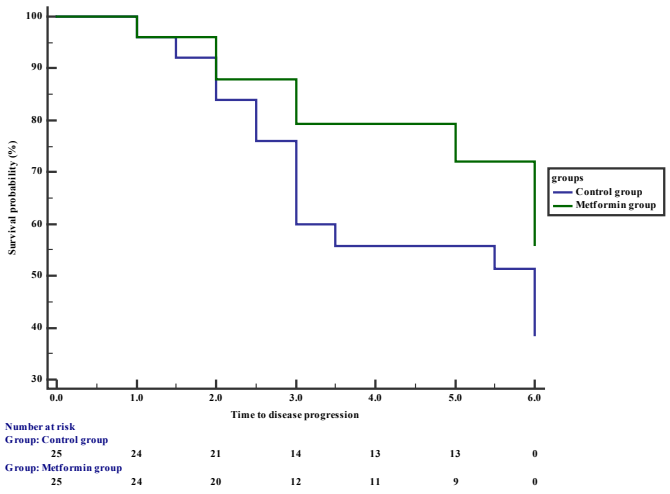

Figure 4: Kaplan-Meier curve of progression free survival

DISCUSSION

The use of metformin is a new trend in cancer trials as many studies support its efficacy against cancer cell proliferation through different mechanisms.

Goodwin et al.[33] reported that metformin did not significantly prolong OS and PFS in nondiabetic metastatic breast cancer cases who were treated with metformin in addition to standard chemotherapy compared with control cases. However, OS and PFS were longer in the metformin group, which may confirm the role of metformin in metastatic breast cancer[34,35]. By contrast, the radiologic response in this study was statistically significantly better in the metformin group than the control group. This difference from Goodwin et al. may be explained by the small sample size of their study and the dose used (850 mg twice daily compared to our 1 g twice daily)[33]. Moreover, participants in the metformin group in Goodwin's study were reported to have higher visceral metastasis; by contrast, in our study, incidence of visceral metastasis was lower (28% vs. 32%) in control and metformin groups, respectively. Furthermore, half the participants in our study had one site for metastasis.

Metformin was accepted by patients under both combination and monotherapy regimens, with prolonged PFS in both groups, compared with the control group, with no statistically significant difference and no synergistic effect for chemotherapy toxicities, except for diarrhea[36,37].

Diarrhea was associated with metformin use as a common side effect, in this study; 36% of patients treated with metformin experienced grade 1 diarrhea, which was tolerable[38]. One of the mechanisms that may cause disturbance in gut motility is the reduction of bile salt absorption[39,40,41] or reduction in serotonin transportation within the gut[42] or both.

Retrospective studies have reported the efficacy of metformin and its association with prolonged OS in patients with type II diabetes mellitus in many types of cancers, including breast[43], lung[44,45], ovarian, and liver cancer. A study on nondiabetic women with breast cancer suggested that metformin exerts its antitumor and antimetastatic effects by reducing levels of oncogenic IGF-1 in circulation.

The perception of metformin as an antitumorigenic and antimetastatic agent arose from its ability to affect energy production and reduce resistance to chemotherapy.

Further clinical trials are warranted to assess the heterogeneous effects of metformin.

CONCLUSION

The findings of our study support heterogeneous effects of metformin on metastatic breast cancer in nondiabetic women as a better radiologic response was obtained for those who used metformin; however, OS or PFS were not significantly affected. Moreover, the hazard of mortality and disease progression was lower in metformin group. Larger studies are needed in this area.

Authorship Contribution:

Hager salah: Corresponding Author, participated in design, analysis and data interpretation, write and review the manuscript.
Hoda Rabea: Author, participated in design, analysis and data interpretation, write and review the manuscript.
Ahmed Hassan: Author, participated in design, analysis and data interpretation, write and review the manuscript.
Ahmed A. Elberry: Author, participated in design, analysis and data interpretation, write and review the manuscript.

Potential Conflict of Interest: None.

Competing Interest: None.

Sponsorship: None.

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